Mathematical model of ion transport in human nasal epithelia: Investigating the pathogenesis of Cystic Fibrosis *in silico*

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Introduction

Cystic Fibrosis (CF) disease results from loss-of-function mutations in the Cystic Fibrosis Trans-membrane conductance Regulator *(CFTR)* gene, which encodes an anion selective channel protein. In the human airways CF mutations lead to disrupted epithelial ion transport, and consequently CF epithelia exhibit abnormal bioelectric properties [1–3]. We have developed a mathematical model of ion and water transport in human nasal epithelial (HNE) cells, which allows us to examine how these abnormal bioelectric properties arise from underlying differences in transport protein activity between the normal and disease states.

Materials and Methods

Mathematical model of ion transport kinetics

We model a mono-layer of HNE cells between two compartments of physiological saline solution (figure 1(a)), representing the environment experienced by HNE cells *in vivo* during clinical nasal potential difference (PD) measurements, or *in vitro* in an Ussing chamber experiment. We consider ion and water transport between the cell and external solutions driven by electrochemical and osmotic gradients. Model components are ENaC & CFTR ion channels in the apical membrane, and K^+ & Cl^- channels, Na^+-K^+ pumps & NKCC1 co-transporters in the basolateral membrane. Differential equations enforce conservation of ions and water, and an equivalent electrical circuit description of the epithelium (figure 1(b)) is utilised to calculate apical and basolateral membrane potentials in the open circuit configuration. The mathematical model is formulated as a system of ordinary differential equations (ODEs), $dx/dt = f(x, P)$. x are cellular variables (volume W, moles of Na^+, Cl^- & K^+, and apical V_m^{ap} & basolateral V_m^{ba} membrane PD), and P are transport parameters (membrane permeabilities, pump / cotransport densities etc):

$$\frac{dW}{dt} = J_w^{ba}(t) - J_w^{ap}(t)$$

$$\frac{dNa^+}{dt} = J_{NKCC}(t) - 3\,J_{NaK}(t) - I_{Na^+}^{ap}(t)/F\,z_{Na^+}$$

$$\frac{dCl^-}{dt} = 2\,J_{NKCC}(t) - \left(I_{Cl^-}^{ba}(t) + I_{Cl^-}^{ap}(t)\right)/F\,z_{Cl^-}$$

$$\frac{dK^+}{dt} = J_{NKCC}(t) + 2\,J_{NaK}(t) - I_{K^+}^{ba}(t)/F\,z_{K^+}$$

$$\frac{dV_m^{ap}}{dt} = -\frac{1}{C_m}\left(I_{Na^+}^{ap} + I_{Cl^-}^{ap} + I_{Na^+}^{pa} + I_{Cl^-}^{pa} + I_{K^+}^{pa} + I_{gluc}^{pa}\right)$$

$$\frac{dV_m^{ba}}{dt} = +\frac{1}{C_m}\left(I_{K^+}^{ba} + I_{Cl^-}^{ba} + z_{Na^+}F\,J_{NaK} + I_{Na^+}^{pa} + I_{Cl^-}^{pa} + I_{K^+}^{pa} + I_{gluc}^{pa}\right)$$

Analysing effect of parameter variations on steady state and kinetic model behaviour

We solve the set of non-linear equations $f(x, P) = 0$ for different sets of parameter values P, and determine how steady state cellular variables such as trans-epithelial potential difference ($V_t = V_m^{ba} - V_m^{ap}$) vary as a function of transport parameters (e.g. $P_{Na^+}^{ap}, P_{Cl^-}^{ap}$). We investigate the transient dynamics of the cellular variables, by numerically integrating the system of ODE's. Two interventions are commonly carried out in

clinical nasal PD measurements and in studies of airway ion transport: addition of amiloride to block ENaC channels, and lowering of [Cl^-] in the external solution. We simulate these experiments *in silico*, by appropriate manipulation of model parameters, and investigate how the model responses depend on transport parameters. We then compare model output with experimental data for steady state and kinetic behaviour of membrane potentials and intracellular concentrations, in order to validate that the model is reproducing the observed physiology accurately. By investigating which regions of parameter space include values that reproduce the observed normal and CF physiological response, we can determine which transport parameters must assume values are different in the two states.

Conclusion

CF is a common genetic disease which disrupts ion transport in several epithelia, causing the most severe consequences in the airways. By devising a mathematical model of ion transport in HNE cells, and using it to estimate physiologically relevant transport parameters from experimental data, we are able to investigate what underlies altered epithelial bioelectric properties in the CF disease state. These insights allow us to shed light on the pathogenesis of CF disease, its diagnosis, and may inform future drug and gene therapies aimed at correcting the ion transport defects in CF patients.

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References

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Figures

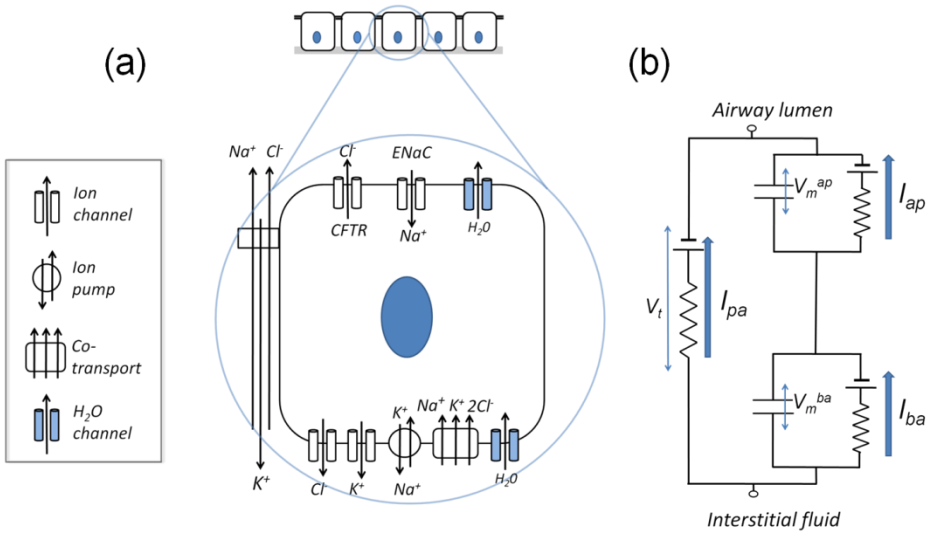

Figure 1: (a) Schematic diagram of cellular model of human nasal epithelial cell, highlighting major trans-cellular and trans-epithelial ion transport pathways. (b) Equivalent electrical circuit description of the airway epithelium in open circuit configuration, the apical and basolateral membrane potentials are coupled via the paracellular conductance.